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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,583	05/03/2002	Dan L. Eaton	10466/350	2698

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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,583	EATON ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/28/2005 has been entered.

Status of Application, Amendments, and/or Claims

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Jon Lockard.

3. The Amendment filed 28 March 2005 has been entered in full. Claims 1-3 have been cancelled, claims 4-5 and12-13 have been amended, and claims 14-17 have been added. Therefore, claims 4-17 are currently pending and the subject of this Office Action.

Inventorship

4. The request for the deletion of an inventor in this nonprovisional application under 37 CFR 1.48(b) is deficient because: Amendment of the inventorship requires, as set forth in CFR 1.48(b)(1):

(1) A request, signed by a party set forth in § 1.33(b), to correct the inventorship that identifies the named inventor or inventor's being deleted and acknowledges that the inventor's invention is no longer being claimed in the nonprovisional application.

Information Disclosure Statement

4. The information disclosure statement (IDS) filed 28 March 2005 has been considered by the examiner.

Withdrawn Objections and/or Rejections

Claim Rejections - 35 USC § 101

5. The rejection of claims 1-3 under 35 U.S.C. §101 as set forth at pages 2-5 in the previous Office Action (mailed 28 December 2004) is moot in view of Applicant's cancellation of said claims (filed 28 March 2005).

Claim Rejections - 35 USC § 112, first paragraph

6. The rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, for lack of enablement due to the invention not being supported by a specific or substantial asserted utility or a well-established utility as set forth at page 5 in the previous Office Action (mailed 28 December 2004) is moot in view of Applicant's cancellation of said claims (filed 28 March 2005).

7. The rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, for lack of enablement as set forth at page 5 of the previous Office Action (mailed 28 December 2004) is moot in view of Applicants cancellation of said claims (filed 28 March 2005).

8. The rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement as set forth at pages 5-6 of the previous Office Action (mailed 28 December 2004) is moot in view of Applicants cancellation of said claims (filed 28 March 2005).

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st Paragraph

9. Claims 4-13 remain and newly added claims 14-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth at pages 2-5 of the previous Office Action (mailed 28 December 2004).

10. Specifically, claims 4-17 are directed to an isolated polypeptide comprising (a) the amino acid sequence of the polypeptide of SEQ ID NO: 74, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 74, lacking its associated signal peptide, (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, (d) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, including its associated signal peptide, or (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203248. The claims are also directed to an isolated polypeptide having at least 95% and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide of SEQ ID NO: 74, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 74, lacking its associated signal peptide, (c) the amino acid

sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, (d) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, including its associated signal peptide, or (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203248; wherein said polypeptide is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor, respectively, or wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor, respectively, or wherein said polypeptide or a fragment thereof can be used to generate an antibody which can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples. The claims also recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide.

11. Applicant's arguments (filed 28 March 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

12. Applicant asserts that Example 18 shows that the mRNA associated with PRO1335 protein is more highly expressed in normal stomach, lung, rectal, and skin tissue compared to stomach, lung, rectal, and melanoma tumors, respectively. Applicants argue that the utilities of PRO1335 polypeptide include the use as a diagnostic tool.

13. Applicant's arguments have been fully considered but are not found to be persuasive. In the instant case, the specification indicates the PRO1335 gene is more highly expressed in normal stomach, lung, rectal, and skin tissue compared to stomach, lung, rectal, and melanoma tumors, respectively (the numerical increase is not known). However, there is no guidance in the

specification as to how high the levels are or to what extent the mRNA is differentially expressed. The disclosure lacks information and guidance to support a specific and substantial use for the claimed invention. Even if tissue samples are pooled, about which the first Grimaldi Declaration says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation there is insufficient guidance. If a clinician took a stomach tissue sample from a patient with suspected stomach cancer, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO:73 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? While the 6th paragraph of the first Grimaldi Declaration says that the detection technique used in the specification makes it "reasonable to assume that any detectable differences seen between two samples will represent at least a two-fold difference in cDNA," that statement still does not answer the questions raised above and does not place a specific and substantial use of the nucleic acid in the skilled artisan's hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of stomach or lung tissue that can used, and other questions, the specification has not provided the invention in a form usable by the skilled such that significant further experimentation was unnecessary. Furthermore, the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (Journal of Proteome Research 2:405-412,

2003) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (pg 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. In contrast, however, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (See discussion section). Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the instant specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. Furthermore, even if Applicants establish a specific and substantial or well-established utility of the PRO1335 polynucleotide of SEQ ID NO:73, there is no evidence regarding whether or not PRO1335 polypeptide levels are also decreased in these cancers.

14. Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then the encoded polypeptide is useful in diagnostics. The Declarations of Grimaldi (second declaration) and Polakis discuss the likelihood that if the nucleic acid is differentially expressed in tumors, then the encoded polypeptide will also be. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to

approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. Applicants also assert that the references of Alberts (Exhibits 1 and 2) and Lewin (Exhibit 3) support the statements of Grimaldi and Polakis.

15. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. While the Examiner agrees with the teachings of Alberts and Lewin that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression, as Alberts (Exhibit 1) also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (See Exhibit 1 at pg 453). Applicants submit Exhibit 5 (Meric et al., 2002) which states the following:

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription.

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (See page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in

the components of the translation machinery (See pages 973-974). While Exhibit 4 (Zhigang et al., 2004) provides an example of a high degree of correlation between protein and mRNA expression, the art also teaches that polypeptide levels cannot be accurately predicted from mRNA levels. As discussed by Haynes et al (1998, Electrophoresis, 19:1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (Journal of Proteome Research 2: 405-412, 2003) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (pg 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that twenty-eight of the 165 protein blots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found ($r = -0.025$), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of

protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance.

16. Given the asserted decrease in PRO1335 mRNA expression, and the evidence provided by the current literature, one skilled in the art would not assume that a small decrease in expression (no quantitative data provided) would correlate with significantly decreased polypeptide levels. Further research needs to be done to determine whether the small decrease in PRO1335 mRNA expression supports a role for the encoded polypeptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

17. Accordingly, the specification's assertion that the PRO1335 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics is not substantial.

18. Applicants note at page 19 of the response (filed 28 March 2005) that the PTO has issued several patents claiming differentially expressed polypeptides.

19. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the current rejection is in compliance with the most currently-published version of the Utility Guidelines which require that all biological inventions must have credible, specific and substantial ("real world") utility. Additionally, each Patent Application is examined on its own merits. The invention that was deemed allowable in one patent has no bearing on this application.

20. Applicants argue at pages 19-21 of the response (filed 28 March 2005) that the arguments made by the PTO are not sufficient to satisfy the PTO's initial burden of offering evidence that one of ordinary skill in the art would reasonably doubt the asserted utility. Applicant states that the Examiner's initial burden is to establish that it is more likely than not that a person of ordinary skill would consider that any utility asserted by the applicant would be specific and substantial. Applicant indicates that all the relevant evidence of record must be considered by the Examiner.

21. Applicant's arguments have been fully considered but are not found to be persuasive. In the previous Office Action of 03 August 2004, the Examiner made a *prima facie* showing that the claimed invention lacks utility and provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (see pages 3-4). Essentially, Applicant has not provided evidence to demonstrate that the PRO1335 polypeptide of the instant application is supported by a specific and asserted utility or a well established utility. The

Examiner has fully considered all evidence of record and has responded to each substantive element of Applicant's response. It is noted to Applicant that MPEP § 2107.02 (part VI) also states that "where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained".

35 U.S.C. § 112, 1st Paragraph (Enablement)

22. Claims 4-13 remain and newly added claims 14-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

23. Additionally, (regarding the recitation of variants 4-5, 12-17) at pages 23-24 of the response (filed 28 March 2005), Applicant states that the pending claims are related to polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:74, and which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, or "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples." Applicant asserts that any person of skill would know how to make and use the invention without undue experimentation based on the teachings in the Specification and the

general knowledge in the art at the time the invention was made.

24. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Furthermore, recitation of the phrases "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used

to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples" in the claims is not adequate to describe the PRO1335 polypeptide or all possible variants that have at least 95% and 99% sequence identity to the PRO1335 polypeptide, since there was no reduction to practice to support the amended claims.

25. Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 112, 1st Paragraph (written description)

26. Claims 4-5 and 12-13 remain and claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth for claims 4-5 and 12-13 at pages 5-6 of the previous Office Action (mailed 28 December 2004).

27. Applicant's arguments (filed 28 March 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

28. Applicants argue at pages 25-27 of the response (filed 28 March 2005) that based on the high percentage of sequence identity, there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:74. Applicants further argue that the pending claims are analogous to the claims discussed in Example 14 of the written description training materials. Lastly, Applicants argue that the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in stomach, lung, rectal or skin tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples.

29. Applicant's arguments have been fully considered but are not found to be persuasive. Applicant's citation of relevant case law at page 25 of the response is noted. The Examiner takes no issue with the case law. Applicant has not described or shown possession of all polypeptides that share 95% and 99% sequence identity to SEQ ID NO: 74, that still retain the function of SEQ ID NO: 74. Nor has Applicant described a representative number of species that share 95% and 99% sequence identity to SEQ ID NO: 74, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 74. Since one skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed PRO1335 polypeptides, one skilled in the art would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making and screening the same for activity or expression

patterns/levels. The claimed product itself is required. Furthermore, recitation of the phrases "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples" in the claims is not adequate to describe the PRO1335 polypeptide or all possible variants that have at least 95% and 99% sequence identity to the PRO1335 polypeptide, since there was no reduction to practice to support the amended claims. Lastly, recitation of "wherein said polypeptide is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively" or "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples" in the claims is not a functional limitation contrary to the Applicants assertion nor does it provide adequate written description of all the possible variants that have at least 95% and 99% sequence identity to SEQ ID NO:74 that are also "more highly expressed" in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal, or melanoma tumor, respectively. Furthermore, the broad-brush discussion of making and screening for variants disclosed in the specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have an activity. The specification's general discussion of making and screening for variants

constitutes and invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. Additionally, the fact pattern of the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the protein and variants have a specific activity disclosed in the specification. However, regarding PRO1335 polypeptides of the instant invention, the specification does not teach any significance or functional characteristics of the PRO1335 polypeptide. Applicants made no variant polypeptides nor have they shown that any PRO1335 polypeptide is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

30. Therefore, only the polypeptide set forth as SEQ ID NO:74, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Summary

31. No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
June 20, 2005

LORRAINE SPECTOR
PRIMARY EXAMINER